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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,578	03/09/2001	Patrick Hwu	2026-4341	6841

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LEYDIG, VOIT & MAYER, LTD.
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6731

EXAMINER
LI, QIAN JANICE

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/803,578	HWU ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/22/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41 and 94-111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41 and 94-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and remarks filed 4/22/08 are acknowledged. Claim 41 has been amended. Claims 110, 111 are newly submitted. Claims 41, 94-111 are pending and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41, 94-111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amended 41 recites “a preselected antigen”, it is unclear the identity of the antigen, and how it is related to the antigens on the allogeneic cell, and/or the chimeric receptor, and thus the metes and bounds of the claims are uncertain.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 41, 94-103, 105, 106, 108-111 stand or newly rejected under 35 U.S.C. 103(a) as being obvious over *Hwu et al* (Cancer Res 1995;55:3369-73, IDS), in view of *Munz et al* (J Immunol 1999;162:25-34), for reasons of record and following.

Hwu et al. teaches a method for preparing tumor reactive lymphocytes comprising **a**). providing murine tumor infiltrating lymphocytes (TIL) transduced with a recombinant retroviral vector (Mov-γ) encoding a chimeric receptor reactive with ovarian adenocarcinoma cells in the presence of IL-2 (e.g. the abstract, and column 2, page 3369), wherein the chimeric receptor comprising a single chain variable region from mAbs joined to the Fc receptor γ chain and capable of mediating T cell receptor signal transduction and binding FBP (e.g. column 2, page 3369), and **b**). the transduced TIL cells were co-cultured with syngeneic MC38 colon tumor cells, which results in a large amount of mIFN-γ production (indicating the TIL cells contain an endogenous T-cell receptor reactive with the syngeneic MC38 cells). The process taught by *Hwu et al* differs from instantly claimed in that the (stimulator) tumor cell in the co-culture is syngenic, not allogenic.

Munz et al. supplemented *Hwu et al.* by establishing that using an allogenic cell as T cell stimulus is comparable to the syngenic/autologous stimulation in obtaining potent tumor reactive CTL cells. *Munz et al.* co-cultured PBL with irradiated allogenic (T2 cells) or syngenic PBL in the presence of IL-2 (left column, page 26), and reported that allogenic APC allows the stimulation of high avidity cytotoxic T cell. *Munz et al.* also taught the need in the art for the allorestricted T cells because the immune system of a cancer patient is often partially destroyed by chemotherapy or factors produced by tumor cells, and under such circumstance, allogenic APCs may be used for tumor antigen-specific T cell activation in immunosuppressed patients (e.g. the paragraph bridging pages 32-33), and concluded with respect to allogenic stimulated T lymphocytes, "SUCH T CELLS MIGHT INDEED BE USEFUL FOR TUMOR IMMUNOTHERAPY" (e.g. abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the preparation process as taught by *Hwu et al.,* with that of *Munz et al.* by co-culturing either syngenic or allogenic APCs with T cells for

activation, with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the benefit as taught by *Munz et al*. Given numerous methods known in the art for T cell activation and expansion, this limitation falls within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

The applicant argues that Hwu et al. does teach selecting and amplifying lymphocytes from a mixed population of cells, but simply co-cultured TILs with MC38 tumor cells.

Applicant's arguments have been fully considered but they are not persuasive.

As an initial matter, it is noted the amended claim 41 adds on step (i), "*selecting and specifically amplifying, from a mixed population of cells, lymphocytes comprising an endogenous receptor that is reactive with a pre-selected antigen capable of inducing proliferation*", wherein the method step of achieving such selection and amplification appears to be the same as previously recited, i.e. "**by** contacting lymphocytes with a cell that is allogeneic to one or more lymphocytes". Since the combined teaching teaches this step as indicated on record, the teaching of *Hwu et al.* meets claim limitation.

Further, it appears the process disclosed by *Hwu et al*. **does** include a pre-selection step, wherein the transduction of TIL was performed on "**antigen-stimulated** TIL" (column 2, page 3369, ¶Lymphocyte Transduction and Cell Culture). Here, the antigen appears to be capable of inducing proliferation of the tumor-infiltrating lymphocytes in the absence of evidence to the contrary.

Accordingly, for reasons of record and set forth *supra*, the rejection stands.

Claim 104 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Hwu et al* (Cancer Res 1995;55:3369-73, IDS), in view of *Munz et al* (J Immunol 1999;162:25-34) as applied to claims 41, 94-103, 105, 106, 108-111 above, and further in view of *Kawakami et al* (USP 5,844,075), for reasons of record and set forth *supra*.

New claim 104 requires that allogeneic:lymphyocyte ratio is about 2:1 to about 5:1, while the cited references do not discuss the ratio. However, such ratio appears to be a routine in the art. For example, *Kawakami et al.* teaches, in the context of expanding antigen-specific T cells, the stimulator:responder cell ratio is between 3:1 to about 10:1 (e.g. § bridging col. 54-55). Here the syngenic/allogeneic cells are the stimulator while lymphocytes are the responder.

Further, considering *Hwu* reference is applicant's own work, and considering the specification is completely silent with regard to discussion about the ratio, the limitation does not appear to be the novel aspect of the claimed invention, and falls within the bounds of optimization, in the absence of evidence to the contrary.

Claim 107 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Hwu et al* (Cancer Res 1995;55:3369-73, IDS), in view of *Munz et al* (J Immunol 1999;162:25-34) as applied to claims 41, 94-103, 105, 106, 108-111 above, and further in view of *Raubitschek et al* (USP 6,41,319), for reasons of record and set forth *supra*.

The combined teaching of *Hwu et al* in view of *Munz et al* fails to specify the rapid expansion protocol as recited in claim 107. *Raubitschek et al.* remedies the deficiency by establishing REP was a well-known protocol for lymphocyte expansion (column 14, lines 18-19).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the REP taught by *Raubitschek et al.,* in the preparation process as taught by *Hwu et al.* in view of *Munz et al.* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so because it is one of the routine procedure for lymphocyte expansion. Given the knowledge of the skilled in the art, this limitation falls within the bounds of design choices. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI, M.D.** whose telephone number is 571-272-0730. The examiner can normally be reached on 9 AM -7:00pm, Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on 571-272-0739. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633

Q. JANICE LI, M.D.
Primary Examiner
Art Unit 16333

QJL
July 17, 2008